Molar pregnancy and risk for cancer in women and their male partners

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OBJECTIVE: It was our aim to evaluate the hypothesis that molar pregnancy is a marker of increased risk for cancer.

STUDY DESIGN: This was a nationwide cohort study of 1520 women, identified from the Danish National Register of Patients, in whom a molar pregnancy was diagnosed during the period 1977-1992 and of 1295 male partners of these women, traced in the Danish Central Population Register.

RESULTS: Linkage of the female roster with the Danish Cancer Registry through 1994 revealed 19 cases of gestational choriocarcinoma, whereas 0.04 was expected from the rates for the general population. Twenty cases of cancers of other types were observed with 24.9 expected (standardized incidence ratio, 0.8; 95% confidence interval, 0.5-1.2), but no specific type of cancer other than gestational choriocarcinoma occurred at a rate significantly different from that expected. Among the 1295 male partners notified in the Central Population Register, a total of 22 cancers were observed with 21.9 expected (standardized incidence ratio, 1.0; 95% confidence interval, 0.7-1.5).

CONCLUSION: Molar pregnancy is not associated with an increased risk for cancer other than gestational carcinoma. (Am J Obstet Gynecol 1999;181:630-4.)

Key words: Hydatidiform mole, maternal cancer, paternal cancer, gestational choriocarcinoma, cohort study

Hydatidiform moles arise in the fetal chorion and are characterized by cystic swelling of the chorionic villi, accompanied by variable trophoblastic proliferation.[1] A complete hydatidiform mole is usually diploid, with a 46,XX karyotype, and all of the molar chromosomes are of paternal origin.[2] Most complete moles develop after the fertilization of an anuclear ovum by a haploid (23,X) sperm, which then duplicates its own chromosomes.[3] About 10% of complete moles have a 46,XY karyotype, which arises from fertilization of an a nuclear ovum by 2 spermatozoa.[4] Although the chromosomes in a complete mole are of paternal origin, the mitochondrial deoxyribonucleic acid is of maternal origin.[5] Partial hydatidiform moles are generally triploid and result from fertilization of an apparently normal ovum by 2 spermatozoa.[6] Fetuses of partial molar pregnancies generally have the features of triploidy, including growth restriction and multiple congenital malformations.[7]

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Thus hydatidiform moles result from an unequal contribution of maternal and paternal chromosomes. Complete moles, in particular, are highly likely to be transformed into gestational choriocarcinomas, although these tumors may also occur after an abortion or a term delivery. It is not known whether genomic instability, an inborn error of gene regulation, or exposure to cytotoxic or mutagenic agents before conception plays a role in the induction of the mole and its associated regression into choriocarcinoma. Cytogenetic studies in humans and long-term studies of the cancer pattern in large groups of persons affected by molar pregnancy may help to resolve these questions.

Therefore in this study we assessed the overall and site-specific cancer incidence in population-based cohorts of women who had experienced a molar pregnancy and of their male partners, and we compared these rates with the appropriate rates of cancer in the general population. Also, we assessed the prevalence rate of choriocarcinomas occurring without a preceding molar pregnancy in Denmark, 1977-1994.

Subjects and methods

We used the Danish National Register of Patients (NRP) and the Danish Cancer Registry to identify women in Denmark who had experienced a molar pregnancy. Since 1977, coded data on patients, diagnoses, and surgical procedures included in the regional inpa-

Table I. Descriptive characteristics of 1520 women with hydatidiform mole in Denmark, 1977-1992

Characteristic	Hydatidiform mole		Pregnancies* (No.)	Rate of molar pregnancy†
	No.	%		
Entire study group	1520	100	1,411,000	1.1
Year of diagnosis				
1977-1981	478	31	451,000	1.1
1982-1886	394	26	407,000	1.0
1987-1992	648	43	553,000	1.2
Age at diagnosis of molar pregnancy				
14-19 y	109	7	95,000	1.1
20-24 y	423	28	375,000	1.1
25-29 y	510	34	489,000	1.0
30-34 y	266	17	293,000	0.9
35-39 y	105	7	122,000	0.9
≥40 y	107	7	37,000	2.9
Type of mole				
Mole, not otherwise specified	916	60	—	—
Abortion of molar pregnancy	581	38	—	—
Extrauterine mole	23	2	—	—

*Sum of live births, stillbirths, induced abortions, and spontaneous abortions (n = 12).
†Per 1000 pregnancies.

tient registration files in Denmark have been converted to a standardized computer format and transferred to the NRP, which is located at the Danish National Board of Health. Over the study period, the register covered >99% of all discharges from nonpsychiatric hospitals.[8] Each discharge record includes the personal registration number, date of discharge from the hospital, surgical procedures, and up to 20 discharge diagnoses coded according to a modified Danish version of the *International Classification of Diseases, Eighth Revision (ICD-8).*[9]

During the period 1977-1992, 1514 women were diagnosed with a mole (*ICD-8* code 634.29), a molar abortion (645.01-09), or an extrauterine mole (631.90). Further information on the type of the mole (eg, whether it was complete or partial) was not available from the files of the NRP. Over the same period a total of 313 women in the files of the Danish Cancer Registry were notified of the presence of a molar pregnancy; 28 of these were not already identified in the NRP. The Cancer Registry, which began reporting incidence data on a nationwide scale in 1943, is tumor- and person-based, and each record includes the personal registration number, date of diagnosis of tumor, and tumor information.[10] Tumors are coded according to a modified Danish version of the *ICD-7* and, since January 1, 1978, also according to the *International Classification of Diseases for Oncology (ICD-O),* which includes a specific code for tumor morphologic type.[11]

Although not included in the list of reportable diseases, hydatidiform mole has been regularly notified to the Cancer Registry since 1978 under tumor morphology codes 9100.0-1. Gestational choriocarcinoma has been notified to the Registry under *ICD-7* code 473.0 and, since January 1, 1978, under tumor morphology codes 9100.3 and 9100.6.

The personal identification number, which is unique to every Danish citizen, incorporates sex and date of birth and permits accurate linkage of information between registries. All 1542 women with a molar pregnancy (1514 from the NRP and 28 [1.8%] from the Cancer Registry) were linked to the Central Population Register for verification of the personal identification number and for information on vital statistics and migration. Fifteen women (1.0%) were excluded from the cohort, 14 because they were residents of the Faroe Islands or Greenland, which are not covered by the Danish Cancer Registry, and 1 because her identification number was invalid. Seven women (0.5%) were excluded because they resided permanently in other parts of the world, leaving 1520 women for active follow-up. The prevalence rate of hydatidiform mole was calculated as the number of women with a molar pregnancy divided by the number of pregnancies in Denmark in the period 1977-1992.[12] Besides being responsible in Denmark for the registration of newborn (live-born and stillborn) children, the National Board of Health maintains nationwide registers of induced abortions and of the subset of spontaneous abortions for which women are hospitalized. The characteristics of the cohort are given in Table I.

The members of the study cohort were linked to the files of the Danish Cancer Registry to ascertain incident cases of cancer. The follow-up period began at the date of termination of the molar pregnancy and ended on the subject's date of emigration (n = 17) or date of death (n = 15) or on December 31, 1994 (n = 1488), whichever occurred first. The numbers of cancer cases observed were compared with the numbers of cases expected; the latter were calculated by multiplying the number of person-years for cohort members by the *ICD-7* specific incidence rates of cancer among Danish women in 5-year age

Table II. Standardized incidence ratios* of gestational choriocarcinoma and other cancer types among 1520 women with a previous diagnosis of hydatidiform mole

Type of cancer	*Observed*	*Expected*	*Standardized incidence ratio*	*95% Confidence interval*
Gestational choriocarcinoma	19	0.04	498	295-786
Time since pregnancy				
0 y	15	0.01	3769	2108-6217
1-4 y	3	0.01	204	41-596
≥5 y	1	0.02	58	1.5-32.5
Other malignant neoplasms†	20	24.9	0.8	0.5-1.2
Digestive organs	1	1.8	0.5	0.0-3.0
Respiratory system	0	1.2	—	0.0-3.0
Breast	9	7.2	1.2	0.6-2.4
Female genital organs†	3	4.9	0.6	0.1-1.8
Urinary system	0	0.5	0.0	0.0-7.0
Skin	3	5.2	0.6	0.1-1.7
Brain and nervous system	2	1.3	1.6	0.2-5.7
Lymphatic and hematopoietic tissues	1	1.3	0.8	0.0-4.2
Other and secondary sites	1	1.5	0.7	0.0-3.7

*Ratios of observed to expected.
†Excluding cases of gestational choriocarcinoma.

groups and calendar periods of observation. Standardized incidence ratios, serving as a measure of the relative risk, and 95% confidence intervals were calculated, with a Poisson distribution assumed of the observed cases of cancer.[13] The occurrence of gestational choriocarcinoma was specifically analyzed among cohort members and compared with the appropriate rates for the general female population of Denmark.

Finally, information from the files of the Central Population Register was used to trace the presumed male partners of the 1520 cohort members.[14] A total of 1296 women (85%) were registered as either married (n = 1224) or divorced (n = 72), whereas the remaining 219 women were registered as unmarried. For women who had been married ≥2 times, the husband of the most recent marriage was chosen. Two of the women had been married to the same man in turn, so that 1295 different male partners were left for analysis. The male cohort was followed up in the Cancer Registry from the date of termination of the molar pregnancy of the index women until their own date of emigration (n = 12) or date of death (n = 3) or until December 31, 1994 (n = 1280). The standardized incidence ratios for cancer and associated 95% confidence intervals were calculated by the same statistical procedures as those used for the female cohort.

Results

The 1520 cases of hydatidiform mole occurred among >1.4 million pregnancies in Denmark in 1977-1992 (16 years), which gives a prevalence rate of 1.1 per 1000 pregnancies or 1 case in 880 pregnancies (Table I). The prevalence rate was found to be 2 to 3 times higher among women aged ≥40 years than among younger women.

The women accrued 14,500 person-years of follow-up with an average of 9.5 years (range, >0 to 18 years). The average age at the time of the molar pregnancy was 27.7 years. Overall, 19 cases of gestational choriocarcinoma were reported among women with a previous diagnosis of a mole, yielding a standardized incidence ratio of approximately 500 (Table II); however, 2 of the 4 women in whom a choriocarcinoma was diagnosed more than a year after a molar pregnancy had spontaneous abortions and 2 term deliveries between the molar pregnancy and the choriocarcinoma. Second moles were not reported in these 4 women. The relative risk for other types of cancer combined (Table II) was nonsignificantly decreased on the basis of 20 observed cases, and no specific type of cancer occurred at a rate that was significantly different from that expected.

During the period 1977-1994, 43 cases of gestational choriocarcinoma were reported to the Danish Cancer Registry (ie, approximately 2 cases per year in a population of 1.3 million women aged 15-49 years). This is equivalent to a prevalence rate of choriocarcinoma of 0.03 per 1000 pregnancies in the general population (1 case in 37,000 pregnancies; Table III). Of the 43 cases of choriocarcinoma, 11 were seen at the time of a term delivery (1 case in about 100,000 newborns) and 13 after a spontaneous or induced abortion (1 case in about 40,000 abortions). As indicated here, 4 of these women had experienced a molar pregnancy several years previously. Of the remaining 19 cases of choriocarcinoma, 15 occurred subsequent to a molar pregnancy (1 case in about 120 molar pregnancies) and 4 occurred in women with no record of a preceding reproductive event.

Table IV shows the standardized incidence ratios of cancer among the 1295 male partners of women with a molar pregnancy. A total of 22 cases were observed, with 21.9 expected, yielding a standardized incidence ratio of

Table III. Descriptive characteristics of gestational choriocarcinoma in Denmark, 1977-1994

Characteristic	*No.*	*Choriocarcinoma*		
		No.	*%*	*Rate**
Pregnancies in national population	1,602,000	43	100	0.03
Predecessor of carcinoma				
Term delivery	1,069,000	11†	26	0.010
Abortion	532,000	13†	30	0.024
Molar pregnancy	1,520	15	35	9.9
Not specified	—	4	9	—

*Per 1000 pregnancies with specific outcomes.
†Of which 2 cases were observed in women with a previous molar pregnancy.

Table IV. Standardized incidence ratios* of cancer among male partners of women with molar pregnancy

Type of cancer	*Observed*	*Expected*	*Standardized incidence ratio*	*95% Confidence interval*
All malignant neoplasms	22	21.9	1.0	0.7-1.5
Digestive organs	3	3.5	0.9	0.2-2.5
Respiratory system	2	3.0	0.7	0.1-2.4
Male genital organs	2	3.1	0.7	0.1-2.4
Urinary system	2	2.0	1.0	0.1-3.7
Skin	5	5.0	1.0	0.3-2.3
Brain	2	1.4	1.4	0.2-5.1
Lymphatic and hematopoietic tissues	5	2.2	2.3	0.7-5.4
Other and secondary sites	1	1.7	0.6	0.0-3.3

*Ratios of observed to expected.

1.0 (95% confidence interval, 0.7-1.6). No remarkable type-specific cancer pattern was seen in comparison with that of the general male population of Denmark.

Comment

Gestational trophoblastic disease encompasses a continuum of tumors that arise in the fetal chorion of the placenta; historically, these have been classified as either hydatidiform mole or gestational choriocarcinoma. They share 3 characteristics—they can be treated successfully by chemotherapy, they produce human chorionic gonadotropin, and they originate in tissue that is genetically different from that of the host. In the current study, which covered the entire female population of Denmark in 1977-1992, we found a prevalence of 1.1 hydatidiform moles per 1000 pregnancies, defined as the sum of live births, stillbirths, induced or reported spontaneous abortions, and ectopic pregnancies. This rate is in the upper end of the range of prevalence rates reported in western Europe[15-17] and North America,[18-20] (ie, from 0.6 to 1.1 cases per 1000 pregnancies). We also observed a twofold to threefold increase in risk for molar pregnancy among women >40 years old, which is compatible with the findings of other studies.[21, 22]

Gestational choriocarcinoma is an extremely rare disease, with 2 to 3 new cases per year in the entire fertile female population of Denmark. The frequency of choriocarcinoma of approximately 0.03 per 1000 pregnancies is close to the frequencies reported from other parts of Europe and from the United States.[23, 24] In our study only about one third (15/43, 35%) of the gestational choriocarcinomas observed in the general female population were preceded by a molar pregnancy, whereas 26% were seen after a term delivery and 30% after an abortion. One remarkable observation was that 4 women had a term delivery or a spontaneous abortion between the molar pregnancy and gestational choriocarcinoma. Although we cannot exclude the possibility that a second mole was unnoticed or at least unregistered, this observation suggests that women with development of a molar pregnancy or gestational choriocarcinoma may carry a genetic predisposition, which is either innate or derived from their male partner.

We were able to identify only one formally conducted epidemiologic study of risk factors for gestational trophoblastic disease[25]; however, no indication of a specific mutagenic exposure of the women was found. If the formation of a molar zygote or the initiation of a gestational choriocarcinoma is facilitated by some kind of genomic instability in the woman or her partner, a molar pregnancy could be a marker of other diseases, including cancer. Apart from the highly increased risk for choriocarcinoma in women who had previously experienced a molar pregnancy, we found no overall or site-specific increased

risk for cancer, either in the women or in their male partners.

The study is limited, however, by a relatively small number of subjects, who were also relatively young at the start of follow-up, strongly reducing the probability of detecting cancers at specific sites. The interpretation of the results is also limited by the short follow-up period, on average, 9.5 years, which may be too brief to measure the outcome of a prolonged pathogenic process such as cancer. The study is, however, countrywide and covers >1.4 million pregnancies over a period of 16 years, including all cases of molar pregnancy and gestational choriocarcinoma.

In summary, our study of women with a molar pregnancy and their male partners revealed no evidence of an increased risk for cancer other than gestational choriocarcinoma.

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